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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/911,826	07/20/2001	Daniela Rotin	DWW-5001	9258

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EXAMINER	
BASI, NIRMAL SINGH	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 01/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/911,826	ROTIN ET AL.	
	Examiner	Art Unit	
	Nirmal S. Basi	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *1-28, 32-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-31 and 36-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Amendment filed 10/21/04 has been entered.

2. **Claim Rejection, 35 U.S.C. 112**

Claims 29-31 and 36-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 29-31, 38 and 40 are indefinite because it is not unclear what specific amino acids comprise of the portion of GRF4 that is stated to be a "CDC25-related GEF domain". How is the CD25 related to the GEF domain? It is suggested to overcome the rejection CDC25-related GEF domain be identified by SEQ ID No:. Applicant states on page 17 of the response that the GRF4 polypeptide was completely unknown prior to this invention. Therefore, it follows if the GRF4 was not known in the art (not an art accepted term at the time of filing on this invention) then domains and motifs contained in the GRF4 molecule can not be envisioned without reference to specific residues in SEQ ID NO:2.

Claims 36-38 is indefinite because it is not clear what sequences comprise the following motifs and domains: a cyclic nucleotide monophosphate binding domain, a Ras exchange motif, a PDZ association domain, a Ras association domain, a CDC25-related GEF domain, first PY motif, second PY motif and a COOH-terminal SaV sequence conforming to a PDZ binding motif. Although an example of a specific amino acid sequence is provided for a cyclic nucleotide

monophosphte binding domain, a Ras exchange motif, a PDZ association domain, a Ras association domain, first PY motif, second PY motif and a COOH-terminal SaV sequence contained in SEQ ID NO:2, it is not clear which other domains and motif sequences are encompassed by claimed domains and motifs so as to allow the metes and bounds of the claim to be determined. Further it is not clear how a SaV sequence conforms to a PDZ binding motif so as to allow the metes and bounds of the claim to be determined. It is suggested to overcome the rejection said domains and motif be identified by SEQ ID NO:. Applicant states on page 17 of the response that the GRF4 polypeptide was completely unknown prior to this invention. Therefore, it follows if the GRF4 was not known in the art (not an art accepted term at the time of filing on this invention) then domains and motifs contained in the GRF4 molecule can not be envisioned without reference to specific residues in SEQ ID NO:2.

Claims 37, 39 and 41 are rejected for depending on an indefinite base claim.

Claim Rejection, 35 U.S.C. 112

3. Claims 29-31, and 36-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying a compound which modulates the interaction of GRF4 (SEQ ID NO:2) with Ras, GRF4 (SEQ ID NO:2) with Rap1, and a method for evaluation the cell proliferation reducing properties of a compound that reduces the binding of GRF4

(SEQ ID NO:2) with Ras, does not reasonably provide enablement for the use of proteins comprising undefined domains and motifs. The, specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While the person of ordinary skill in the art would, in light of the specification be able to isolate and use GRF4 (SEQ ID NO:2), Ras and Rap1, the scope of the claims, which encompass polypeptides with undefined domains and motifs which may be unrelated to said motifs present in the GRF4 of SEQ ID NO:2, encompass mutants, variants, analogs (derivatives) are not enabled by the disclosure. The disclosure does not teach how to make such derivatives or to use a commensurate number of such derivatives which may act in a different manner to the native proteins. The claims encompass derivatives of GRF4 interacting with Ras and Rap1. The specification disclose specific GRF4 domains and motifs, contained in SEQ ID NO:2, arranged in a specific order, which are required for functionality. Derivatives of GRF4, although containing one or more of the domains or motifs may not function as the native and modulate interaction with Ras or Rap1 and affect cell proliferation. Further, there is no disclosure of the critical structural feature of the GRF4 that is required for Ras or Rap1-binding or how structure relates to function. Due to the large quantity of experimentation necessary to make or identify the derivative of GRF4 for use of instant invention, the lack of direction/guidance presented in the specification regarding the identification, purification, isolation and

characterization of said derivatives and binding fragments, the unpredictability of the effects of mutation on the structure and function of proteins (since mutations of SEQ ID NO:2, are also encompassed by the claims), and the breadth of the claim which fail to recite specific structural and functional limitations for the production of active GRF4, undue experimentation would be required of the skilled artisan to make or use the claimed invention in its full scope. Further the name "GRF4" provides no structure to the claimed protein.

While the person of ordinary skill in the art, would, in light of the specification, be able to make polypeptides of SEQ. ID. NO:2, the scope of the claims, which encompass any polypeptide which can be loosely classified as GRF4 is simply not enabled by the disclosure. The disclosure does not teach how to use any of the numerous polypeptides or variants, which are encompassed by the claims, but are inactive or lack functionality.

The claims encompass compounds whose scope cannot be determined due to indefiniteness of the claims (see rejection, above) . Further, structural features that could distinguish the compounds in the genus from others are missing from the disclosure. There is no disclosure of the critical technical feature of the invention. The prior art teaches that amino acid substitutions produce unpredictable results in a structurally related protein. Furthermore, neither the specification nor the prior art provide any guidance as to which amino acids could be altered, nor does the specification provide any guidance as to how the skilled artisan could use an inactive variants, mutants. Therefore, it would require

undue experimentation to practice this invention as claimed, because the skilled artisan would have no reasonable expectation that variants and mutants could be used for any purpose. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to make, isolate, identify and use the claimed variant nucleic acid encoding polypeptides encompassed, without undue experimentation.

Pertaining to claims 39, and 41, while one of skill in the art can readily envision numerable species of polypeptide sequences that are at least a given % identity to a polypeptide at least a given % identity to a recited reference amino acid sequence, one cannot envision which of these comprise a polypeptide with a specific activity of the protein of SEQ ID NO:2. The fact remains that the actual protein with a particular activity or the actual amino acid sequences of such a protein *cannot* be envisioned any better when the possible choices are narrowed from all possible sequences to all possible sequences with an arbitrary structural relationship with a known functional sequence. For example, if one skilled in the art were to make a synthetic polypeptide with 90% identity to the reference amino acid sequence, he would be no more able to say whether it was a functional polypeptide than if the polypeptide was only 10% identical to the reference polypeptide sequence. Nor would he be able to say whether the sequence existed in nature.

To put the situation in perspective, the number of possible amino acid sequences of 100 amino acids in length is 20^{100} (approx. 10^{130}. The number of possible amino acid sequences that are of a given %identity relative to a

reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following formula:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + \ldots + X^{n-1}L(L-1)(L-2)\ldots(L-(n-2))/(n-1)! + X^nL(L-1)(L-2)\ldots(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence, L is the length of the reference sequence, n is the maximum number of residues that can be inserted, deleted or substituted relative to the reference sequence at a given % identity. For an amino acid sequence, X is 19 (alternate amino acids).

For a 100 amino acid sequence that is at least 90% identical to a reference sequence of 100 amino acids, the number of possible sequences having 9 amino acid substitutions relative to the reference (the penultimate term of the formula) is approximately 6×10^{23}. Whereas the number of possible sequences having 10 amino acid substitutions relative to the reference (the final term of the formula) is approximately 1.1×10^{26}. So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total. It can also be shown that N can be approximated by the formula $X^nL^n/n!$, where $n<<L$. Using this formula to approximate N in this example gives a value of 1.7×10^{26}.

In the present case, the reference amino acid sequence, SEQ ID NO 2, is 537 amino acids long. Using the approximation formula, the number of possible amino acid sequences and nucleotide sequences that are at least e.g. 80% identical to the reference amino acid sequence or nucleotide sequence, would be

much larger than 6×10^{23} and 1.6×10^{56}, respectively. While limiting the scope of potential sequences to those that are at least e.g. 80% identical to a reference greatly reduces the number of potential sequences to test, it does not do so in any meaningful way. All of these values greatly exceed the estimated number of atoms in the universe (10^{70} to 10^{90}). Thus, limiting the claims by the recited structural relationships merely reduces the degree of impossibility of making and testing sequences for those which encode a functional protein encompassed by the claims.

The specification does not provide any information on the minimal number and specific amino acid residues are necessary and sufficient for a functional activity. The specification also provides no teachings on what amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in an active GRF4 protein that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein. Apart from the motifs and domains present in GRF4 of SEQ ID No:2 is not possible to even guess at the amino acid residues which are critical to its structure or function based on sequence conservation. Therefore one cannot predict variant amino acid sequences for a biologically active polypeptide. Rather one must engage in "case to case painstaking experimental study" to determine active GRF4 variants. Consequently, excessive trial and error experimentation would have been required to identify the protein derivatives of GRF4 that area biologically active since the amino acid sequence of such polypeptides could not be predicted.

The specification discloses only one putative amino acid sequences, SEQ ID NO:2, for a polypeptide having the necessary properties for the disclosed uses, and provides no guidance on obtaining functional polypeptide variants of SEQ ID NO:2, without undue experimentation, which would be suitable in claimed methods.

4. Claims 29-31 and 37-41 remain are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

The claims are directed to method using derivative of GRF4, in methods to identify compounds that modulate GRF4 interaction or have cell proliferation reducing properties.

The specification discloses the polypeptide of SEQ ID NO:2 (GRF4), and prior art Ras and Rap1. The instant disclosure of GRF4 (SEQ ID NO:2) polypeptide does not adequately describe the scope of the claimed genus, which encompasses the use of a substantial variety of subgenera including full-length, truncated, fusion molecules, derivatives and variants of GRF4. A description of

a genus of polypeptides may be achieved by means of a recitation of a representative number of polypeptides, defined by an amino acid sequence, falling within the scope of the genus or of a recitation of structural and functional features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The instant specification fails to provide sufficient descriptive information, such as definitive structural and functional features of the claimed genus of polypeptides and polynucleotides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. The fusion polypeptides, fragments, derivatives and variants encompassed by the claims do not disclose the critical technical feature of the claimed invention or its relationship to function. For example, polypeptides comprising an undefined CDC25-related GEF domain may be completely unrelated to the disclosed polypeptide of SEQ ID NO: 2, having a different function or even be inactive. GRF4 polypeptides comprising a sequence which has at least 80% sequence identity to SEQ ID NO:2 and comprising an undefined CDC25-related GEF domain encompasses billions of variants (see rejection above)domain may be completely unrelated to the disclosed polypeptide of SEQ ID NO: 2, having a different function or even be inactive. The critical technical feature encompassed by the fragments and variants must relate to the encompassed polypeptide, structurally and functionally to the disclosed proteins of SEQ ID NO:2. The same argument applies to the mutants, variants, analogs, homologs, derivatives and

fusion products encompassed by the claims. It is not clear what critical technical feature undisclosed amino acids, disclosed amino acids in a specific fragment, or recited descriptive language provide so as to show a written description of the invention in full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing. There is no description, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

The specification further fails to identify and describe the regulatory regions essential to the function of the claimed invention, which are required since the claimed invention currently encompasses the full length, truncated, fusion products, derivatives and variants thereof. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus may be highly variant, the disclosure is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

An adequate written description of a protein or nucleic acid molecule requires a precise definition, such as by structure, formula, chemical name, and physical properties, not a mere wish or plan for obtaining the claimed chemical invention. Accordingly, an adequate written description of a polypeptide is more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the polynucleotide or the encoded protein itself. Accordingly, the specification does not provide a written description of the invention of claims 29-31 and 37-41.

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe, enable and use the genus as broadly claimed. The skilled artisan cannot envision the detailed chemical structure of the encompassed proteins and, therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. It is acknowledged that the skill of the artisan in the molecular biology art is high. However, in the current instance, the critical special technical feature (structure) of the polypeptides required for interaction is not disclosed. Because of the lack of guidance in the prior art and current application, one skilled in the art could not predict if the variants or derivatives polypeptide of SEQ ID NO:2, have the same activity as the protein of SEQ ID NO:2. The breadth of the claim come from encompassing polypeptides fragments or derivatives variants which do not have an associated structure

which defines the critical special technical feature of the invention. Further the name GRF4 does not even provide any structural information about the claimed polypeptide but claims every protein with Ras or Rap1 binding properties.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid or polypeptide is itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an

adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

With the exception of SEQ ID NO:2 the skilled artisan cannot envision the detailed chemical structure for the use of the claimed polypeptide and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not achieved. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGFs were found unpatentable due to lack of written description for the broad class.

Therefore, only the use of the polypeptide SEQ ID NO:2 in the methods of claims 29-31 and 37-41 but not the full breadth of the claim meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded

that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115). Methods for using derivatives, mutants and variants.of SEQ ID NOS:2 also do not meet written description for the reasons given above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 571-272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-272-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nirmal Basi
January 10, 2005

MICHAEL PAK
PRIMARY EXAMINER